CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-900

Bioequivalence Review(s)

Orig

SUMMARY OF NDA

DATE SUMMARY COMPLETED: May 4, 1972

NDA #17-072

NAME OF DRUG: Trade - Benzedrine Tablet

Generic - d,l amphetamine sulfate

SPONSOR: Smith, Kline and French, Philadelphia, Pa.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION: 5 mg and 10 mg/tablet for oral use.

CATEGORY OR USE OF DRUG: Anorexic agent.

DATE OF AND REASON: In response to FEDERAL REGISTER Notice 35:12652 of 8/8/70.

MATERIAL REVIEWED: Volumes 1.1, 1.11, and 1.12.

RELATED NDA: 17-071 (Benzedrine spansule - SKF)

CLINICAL EVALUATION:

Background: Since Benzedrine (d,l amphetamine sulfate) was marketed in 1936, the sponsor (SKF) believes that Benzedrine, being the first available amphetamine, is not a "new" drug and that an approved NDA is not required, for the product's continued marketing. Thus, this NDA 17-072 is not the usual presentation of new data from controlled studies, but rather it is a summary of clinical studies published during the years of clinical use.

The present review will be limited to the material contained in Volumes 1.1, 1.11, and 1.12, pertaining to the use of Benzedrine "as a short term adjunct in a regimen of weight reduction based on caloric restriction."

Medical Literature:

1. R. H. Kunstadter, M.D.: Experience with Benzedrine Sulfate in the Management of Obesity in Children. J. Pediat. 17:490-501 (Oct.), 1940.

   This study comprises a group of 30 obese children ranging from 2-1/2 to 16 years of age, from both clinic and private practice. There were 14 males and 16 females.

   Dosage: Initial dose = 5 mg; then, it was increased gradually to what was considered an optimal effective dose. The drug was administered either b.i.d., or t.i.d. The majority received a daily dose of from 10-30 mg.

   Results: 26 children received the drug for periods of from 3 weeks to six months. The average weekly weight loss was 0.831 lbs. The greatest weight loss occurred during the first 2 weeks of Rx.

Untoward Reactions (12/26 = 40%):

Dizziness	-	17%
Abdominal pain	-	17%
Headache	-	10%
Insomnia	-	10%
Nausea or vomiting	-	10%
Nervousness	-	7%
Fainting	-	3%
Substernal pain	-	3%

Tolerance to the drug developed frequently, requiring gradual increase in the dose.

2. R. B. Chrisman and William Maury: Benzedrine Sulfate in Obesity. J. Tenn. State Med. Assoc. 34:337-339 (Sept.), 1941.

27 obese patients (1 male) were given benzedrine sulfate (20mg/dy maximum) without dietary restrictions for periods ranging from 2-14 weeks. The average weight loss was 2 lbs./wk. There were two failures. A few patients had transitory sleeplessness and dryness of the mouth.

3. F. K. Albrecht: The Use of Benzedrine Sulfate in Obesity. Ann. Int. Med. 21:983-9, 1944.

Benzedrine sulfate (10-30 mg/day in divided doses) was administered to 300 obese patients (ages 21-53 years) for 2-8 weeks. The average weekly weight loss while taking the drug was 4.24 lbs. for the males and 3.94 for the females. The weight loss is not permanent; it is transient in the great majority of instances and returns when the drug is discontinued unless the patient remains on his special diet.

Untoward Reactions:

Palpitation	-	12%	(Severe in 4%)
Headache	-	32%	
Dryness of mouth	-	56%	
Anxiety	-	14%	
Euphoria	-	22%	
Insomnia	-	4%	

4. S. William Kalb: Amphetamine (Benzedrine) Sulphate and Thyroid Extract in the Rx of Obesity: Observations on 500 cases. J. Med. Soc. N. J. 39:74-75 (Feb.), 1942.

500 patients who were 10-125% overweight were placed on low-caloric high-protein diets ranging from 800 to 1500 calories daily. The patients were weighed weekly for at least 16 weeks. During this period of observation, the patients received in addition to the submaintenance diet at intervals of 4 weeks: (a) Benzedrine 20 mg, (b) thyroid extract 180 mg (Parke-Davis), (c) benzedrine and thyroid

extract, or (d) placebo. Weight loss was greatest during the first 4 weeks of Rx regardless of the kind of medication employed. Mean weight loss per week for each of the groups studied was as follows:

Benzedrine - 2.5 lbs.
Thyroid - 2.6 lbs.
Combination - 2.6 lbs.
Placebo - 2.4 lbs.

Thus, benzedrine failed to accelerate weight loss over that resulting from the submaintenance diet alone.

5. David Adlersberg and Martin E. Mayer: Results of Prolonged Medical Rx of Obesity with Diet alone, Diet and Thyroid preparations, and Diet and Amphetamine. Mt. Sinai Hospital, New York (March 1949.

90 patients (6 men and 84 women) ages 15 to 64 years were treated at first with a 1200 calorie diet for 1.2 to 5.2 months. The average monthly loss of weight during this time varied from 0.3 to 1.9 lbs. In a second period of 2.7 to 11.8 months, the same diet was combined with oral administration of 5 to 10 mg of benzedrine b.i.d.; the average monthly loss of weight ranged from 1.1 to 1.8 lbs. The long-term results with diet alone compared favorably with those obtained with diet and benzedrine.

The stimulating effects of benzedrine were noted by the patients, who occasionally increased the dose of the drug without consulting the physician. Increasingly larger doses were needed for the maintenance of the desired effects on mood and feeling of well-being. Two instances of poisoning were observed. Two psychoneurotic women raised the dose of benzedrine to 100 mg per day because of depression. In both instances the results were extreme irritability and restlessness, insomnia, tachycardia and rapid respiration.

6. Karl H. Beyer: The Effect of Benzedrine Sulfate on Metabolism and the CVS in Man. Univ. Wisc. Med. School, 1939.

Benzedrine sulfate, 30 mg orally, increased the normal metabolic rate an average of 15.4% within the first 2-1/2 hours. The rate returned to normal within 24 hours.

The maxima of the BP effects were reached in 1-1/2 hours following which there was a slow decline in the pressures, reaching the original levels within 24 hours.

7. E. H. Ellinwood, Jr., : Assault and Homicide Associated with Amphetamine Abuse. Amer. J. Psychiat. 127:1170-5 (March), 1971

Mrs. C., a 32 year old woman shot her paramour. Amphetamines, originally, were prescribed to help her lose weight. However, she soon discovered that they relieved her loneliness and depression. Gradually, over a

period of 18 months, she increased the dose to 400-600 mg per day. Hallucinations were not infrequent. She became suspicious. At the time of the shooting, she was taking 600-1200 mg amphetamines per day. Thirteen months after the shooting, Mrs. C. was completely lucide, without any psychotic manifestations.

Amphetamine abuse appeared to be directly related to the induction of violence. The homicidal act was directly related to amphetamine induced paranoid thinking.

CONCLUSIONS:

1. Benzedrine (amphetamine sulfate) is a racemic mixture of the dextro and levo isomers of amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Colton, et al, (Am. J. Med. Sc. 1943) proved experimentally that d-amphetamine (dexedrine) is the main appetite depressant factor in benzedrine.

2. Benzedrine (amphetamine sulfate) is not recommended for use as an anorexiant because it has a more pronounced effect on the CV System than dextroamphetamine (dexedrine).

3. Moreover, because of its significant potential for abuse and tolerance, benzedrine no longer has a valid place in the treatment of obesity.

4. The indications for the use of benzedrine are limited to narcolepsy and minimal brain dysfunction in children.

RECOMMENDATION:

There is no justification for continuing the use of benzedrine in the modern practice of treating obesity. Benzedrine ("bennies") has harmed people much more than it has helped them. Therefore, it is suggested that a "non-approvable" letter issue.

Theresa T. Woo, M.D.

cc:
Orig.

cc: [Orig., Dup., BD-100, BD-120
BD-120/CKennedy

NDA: 17-072 REVIEW OF NDA 1/3/73

SPONSOR: Smith, Kline & French
Philadelphia, Pa.

NAME OF DRUG: Trade - Benzedrine Tablet

Generic - d,l amphetamine sulfate

DOSAGE FORMS AND ROUTE OF ADMINISTRATION: 5 & 10 mg. tablets

CATEGORY: CNS Stimulant

DATE, TYPE AND REASON FOR SUBMISSION: NDA Orig. Amendment - 4/6/72; Response to FR Notice of 8/8/70.

MATERIAL REVIEWED: Medical Officer Review of 5/4/72; Data in the NDA on Narcolepsy(as pertains to children) & Data in the NDA on Minimal Brain Dysfunction. (Vols. 1.7-1.10); NDA 17-071 Vol 2 1(Benzedrine Spansule)--FPL

BACKGROUND INFORMATION:

Dr. T. Woo's MOR states: "Since Benzedrine (d,l amphetamine sulfate) was marketed in 1936, the sponsor (SKF) believes that Benzedrine, being th first available amphetamine, is not a 'new' drug and that an approved NDA is not required, for the product's continued marketing. Thus, this NDA 17-072 is not the usual presentation of new data from controlled studies, but rather it is a summary of clinical studies published during the years of clinical use."

Dr. Woo's recommendations for the use of Benzedrine in obesity were: "There is no justification for continuing the use of benzedrine in the modern practice of treating obesity. Benzedrine ('bennies') has harmed people much more than it has helped them. Therefore, it is suggested that a 'non-approvable' letter issue."

CLINICAL EVALUATION:

A. Use of Benzedrine in Narcolepsy:
This medical officer is responsible for the reviews of psychoactive drugs in the pediatric age group; however, all of the material was reviewed for completeness. The material submitted consists entirely of clinical literature and summaries. Most of the literature contains individual opinions or statements about the efficacy of the use of Benzedrine without supporting data or the summary of individual patients. Only one "controlled" study was submitted and no double-blind studies were included.

It is recognized that a double-blind parallel group design would be difficult, perhaps impossible, because of the small number of patients with diagnosed narcolepsy; however, a double-blind crossover design using the patient as his own control would appear to have been feasible and reasonable. This design was not included.

NAS/NRC apparently did not review Benzedrine since it did not have an NDA; however, the amphetamines, in general, have been published in the Federal Register as being effective for the indication of Narcolepsy. The medical officer review of this NDA for the stated indication appears to be an academic exercise since there apparently is no reason for a decision on efficacy.

The only "controlled" study is described as follows:

Title of Article: "The Use of Benzedrine For the Treatment of Narcolepsy"

Authors: Myron Prinzmetal, M.D. & Wilfred Bloomberg, M.D.

Design: "Single-blind", 1-3 days baseline physiological solution of sodium chloride (because of salty taste of medications) followed by "varying doses of benzedrine", followed by "equivalent doses of ephedrine sulfate" and ending with Benzedrine again. Dosage of benzedrine varied.

Results: "In all instances complete relief from the attacks of sleep, and practically complete relief from cataplexy, resulted when suitable doses of benzedrine were given. On an average, this compound was approximately three times as effective as ephedrine. In four instances huge single doses of ephedrine, as high as from 80 to 150 mg. failed to give relief, while moderate doses of benzedrine, such as 30 mg., afforded complete relief from symptoms. In only one instance did ephedrine prove as effective as benzedrine; in no instance did it prove more effective. No diminution in the effectiveness of benzedrine has been observed as a result of its use over comparatively long periods of time."

Adverse Effects: Insomnia, hyperexcitability, mild restlessness, "evidence of overstimulation of the CNS, as manifested by dilated pupils and inability to relax."

Medical Officer Comments:

1. No double-blind studies were included in the literature submission.
2. Some of the submitted articles were historical in nature, stating the efficacy of benzedrine in narcolepsy without supporting clinical data.
3. Most articles were uncontrolled administration of medication to small numbers of individual patients.
4. Only 1 study was "controlled" and this was not double-blind. It was summarized above and the Sponsor's summary chart is included, in part, on the following page(3)

PRINZMETAL/BLOOMBERG STUDY
(Benzedrine in Narcolepsy)

Case #	Age Sex	Duration of dis.	Cataplexy	Sleep Attks. Daily	Daily Dose Ephedrine	Efficacy	Daily Dose Benzedrine	Efficacy
1	16 M	1 yr.	Yes	3-6	----	----	30 mg.	"Complete relief"
2	21 M	6 yrs.	No	2-4	92 mg	"Complete relief for one	20	"Complete relief"
3	19 M	3 yrs.	Yes	3-4		month, then gradual decline: end of 3 months slight relief."		
(3						"Complete relief of sleep attacks nearly complete of cataplexy."	75 mg	"Complete relief of sleep attacks; nearly complete of cataplexy."
4	24 F	10 yrs.	Yes	3-6	244	"At least one sleep attack daily."	90	"Complete relief."
5	11 M	2 yrs.	No	3-5	48	"At least one sleep attack	24	"Complete relief"
6	34 M	10 yrs.	Yes	2-5	187	daily."		
(6						"only rarely a full day without an attack"	10	"Complete relief"
7	18 M	3 yrs.	Yes	6-10	-	-	40	"Complete relief"
8	14 F	3 yrs.	Yes	3-6	92	"Rare attack"	80	"Rare attack"
9	21 F	4 yrs.	Yes	3-6	244	"At least one attack daily"	70	"Complete relief."

B. Use of Benzedrine in Minimal Brain Dysfunction:

Two volumes of this NDA include copies of articles concerning the use of Benzedrine in children and which the Sponsor indicates is information regarding use of Benzedrine in "Minimal Brain Dysfunction." While these articles do refer to "hyperkinetic" children, ~~xhexxxxxxxxxxxx~~ there is a question of whether they would be considered to have Minimal Brain Dysfunction or primary psychiatric disturbance. ~~XXXXX~~ It is recognized that Minimal Brain Dysfunction is a syndrome which is quite controversial. ~~x~~ The syndrome is characterized by behavioral manifestations (e.g. hyperactivity, impulsivity, short attention span, distractibility) which may or may not be accompanied by learning disabilities, minor neurological signs and abnormal EEG. Children are generally described as being of normal or above average intelligence. In the Conference on the Use of Stimulant Drugs in the Treatment of Behaviorally Disturbed Young School Children it is pointed out that similar behavioral symptoms may be due to other illnesses or to relatively simple causes. Special dysfunctions such as"certainepilepsies, schizophrenia, depression or anxiety, mental retardation or perceptual deficiencies " should be distinguished.

A preliminary draft of material prepared for publication in The Medical Letter(Feb. 8, 1972) makes the following statement: "There are no adequately controlled long-term studies of the use of stimulants in children with IQ's in the normal range who have no abnormal neurological signs and are not in institutions; and it is in such children that the diagnosis of 'minimal brain dysfunction' is most often made..." In this draft it is stated: "Until a more precise definition is agreed upon, the use of sympathomimetic agents should be limited to children under the age of 12 with carefully defined indications. These indications should include all of the following: increased and increasing physical activity apparent in the physicians Office as well as in the classroom; a degree of hyperactivity and inattention that seriously interferes with the child's learning experience and social adjustment; and no obvious cause for this behavior in the school or family setting."

To eliminate some of the heterogeneity of the patient population for purposes of clinical trials in children with "Minimal Brain Dysfunction", the population studied preferably should be children of normal or above normal intelligence, should not have primary psychiatric disturbances or obvious casses for his abnormal behavior in his classroom or family environment(including psychiatric disturbance of the parent). Foster children and adopted children, because of their higher incidence of psychiatric disturbances, if included in clinical trials should be analyzed separately.

The Sponsor describes four (4) studies as being "Controlled Clinical Studies". Three of these studies are not double-blind(Bradley, Lindsley & Korey). It is incomprehensible as to how the Sponsor considered these "controlled" studies since it is generally agreed by experts in~~x~~ the field that double-blind, placebo controlled studies are an absolute necessity for clinical studies in MBD.

The fourth "controlled" study is a double-blind comparison of thioridazine, amphetamine and placebo in institutionalized, "Mentally Deficient" children. These children had been in a psychiatric hospital for children for at least one year. Only 6 children received amphetamine.

It is interesting to compare the summary by the Sponsor(vol. 1.1) with the actual article and summary by the investigators/authors (Alexandris & Lundell--vol. 1.9). It will be noted that the Sponsor's summary obviously distorts the true results of this particular study.
The Sponsor states: "..amphetamine provided significant improvement on 6 of the 14 items of the rating scale - concentration, attention, comprehension, work interest, reading, and class standing; thioridazine produced significant improvement on all 14 items; and placebo produced no significant improvement on any of the items."

The actual article taken from Canad. Med. Ass. J., Jan 13, 1968, vol. 98, p. 95 contains a tablex of the Average Change Scores and Significant Levels for the 14 Items Observedx for Thioridazine, Amphetamine and Placebo(Table I); however, it also contains another Table(Table II) which is not mentioned by the Sponsor and is entitled: "Comparisons of the Effects of Thioridazine, Amphetamine and Placebo on the 14 Items Observed (Duncan Multiple Range Test Results)." This latter Table contains the same 14 items as Table I
The authors state:
"Perhaps the most notable feature of Table II is that there is no significant difference among the three drugs in regard to reading, spelling and arithmetic. The average change score for thioridazine is significantly superior to amphetamine for concentration, aggressiveness, sociability, interpersonal relationship, comprehension, work interest and work capacity. Thioridazine is superior to placebo for all items under observation except reading, spelling and arithmetic. The average change score for amphetamine is superior to placebo in only two respects--comprehension and work interest."

In their Final Summary, the Authors state: "Thioridazine, amphetamine and placebo were evaluated under double-blind conditions in 21 patients (aged 7 to 12 years) who exhibited the hyperkinetic behaviour syndrome. The results indicate that all three drugs favourably influenced various clinical characteristics of the behaviour syndrome. Thioridazine, however, proved to be statistically superior to amphetamine and placebo; amphetamine showed only slight difference from placebo."

Medical Officer Comments:

1. Effects of amphetamine in institutionalized, mentally deficient children cannot be generalized to the usual concepts of children with "Minimal Brain Dysfunction."
2. Only 6 children received"amphetamine"(Benzedrine is not specified) Results as reported by the authors--but not by the Sponsor did not show statistical superiority of amphetamine to placebo.

"no significant difference" with respect to reading, spelling and arithmetic

OVERALL MEDICAL OFFICER OBSERVATIONS:

1. The Sponsor claims that Benzedrine is not a new drug and that an approved NDA is not required.

2. Data contained in this NDA are considered insufficient to establish evidence of efficacy for the indications of Narcolepsy and Minimal Brain Dysfunction. In the case of Narcolepsy, special considerations may be necessary. For Specific details see Medical Officer Comments on page 2.

3. Data contained in this NDA concerning Minimal Brain Dysfunction are inadequate for establishing efficacy for the following reasons:

   a. Three of the Four "Controlled" Clinical Studies(Articles from the literature) are NOT Double-Blind. At this stage(and as far back as the 60's) it has been generally agreed and pointed out in the literature that double-blind, placebo controlled studies are essential for clinical trials in children with MBD.

   b. The fourth "controlled" study contained only 6 patients who received "amphetamine." Results did not show superiority of amphetamine to placebo statistically. Patients were institutionalized, "Mentally deficient" children.

4. Adequately controlled long-term studies of the use of Benzedrine in children are not available.

5. Because of #2 & 3, a review of the labeling was not considered approxpriate by this Medical reviewer since adequate labeling cannot be based on inadequate information.

6. The amphetamines have been published in the Federal Register as being effective for both Narcolepsy and Minimal Brain Dysfunction. While Benzedrine may, in fact, be effective for MBD, the data included in this submission dwe inadequate for substantiation.

7 In view of Observations #s 1, 2, 3 4, 5, & 6 this Medical Officer Review should be referred to Supervisory Staff for their information and final decision re: disposition of this NDA and NDA 17-071, vol. 2.1.

RECOMMENDATIONS: See Medical Officer Observation #7.

Carol Kennedy, M.D.

Carol Kennedy, M.D.

REVIEW OF SUPPLEMENT

DATE COMPLETED: 9-17-79

ANDA #: 83-900/S-005
S-006

CO. NAME: Smith Kline & French Labs.
Philadelphia, PA 19101

NAME OF DRUG: Trade: Benzedrine Tablets

Generic: Amphetamine Sulfate Tablets

DATE OF SUBMISSION: S-005 12-20-78 Labeling revision
S-006 2-6-79 Labeling revision

TYPE OF SUBMISSION: Supplement - name distributor

CLINICAL EVALUATION:

1. Container labels: Satisfactory
   S-006 10 mg. tablets bottles of 100

2. Insert labeling: Satisfactory
   date: Nov. 78 S-005

CONCLUSION: Labeling is satisfactory for the safe and effective use of this product.

RECOMMENDATIONS: Approve supplements S-005, S-006.
S-008

V.V. Karusaitis, M.D.

cc:dup
VVK/wlh/9-18-79

S-008 12-14-79 Labeling revision
Sale Tablets Bottle of 100 Satisfactory

REVIEW OF SUPPLEMENT

DATE COMPLETED: 4-2-80

ANDA #: 83-900/S-009

CO. NAME: Smith Kline & French Labs.
Philadelphia, PA 19101

APPROVAL DATE: 2-26-76

NAME OF DRUG: Trade: Benzedrine

Generic: Amphetamine Sulfate

DATE OF SUBMISSION: 2-29-80

TYPE OF SUBMISSION: Supplement - labeling revision

CLINICAL EVALUATION:

1. Container labels: Satisfactory CII
10 mg. tablets bottles of 100

2. Insert labeling: Not submitted

CONCLUSIONS: labeling is satisfactory for the safe and effective use of this product.

RECOMMENDATIONS: Approve supplement S-009.

V.V. Karusaitis, M.D.

cc:dup
VVk/wh/4-4-80